Risk of Malignant Mixed Mullerian Tumors After Tamoxifen Therapy for Breast Cancer

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Recent studies have indicated that the tamoxifen-related risk of uterine corpus cancer may be especially high for some uncommon cell types, although the magnitude of risk has not been quantified. We evaluated data from 39 451 breast cancer patients diagnosed from 1980 through 2000 who were initially treated with tamoxifen and found that the overall risk of subsequent uterine corpus cancer was increased more than twofold (observed-to-expected ratio [O/E] = 2.17, 95% confidence interval [CI] = 1.95 to 2.41) relative to the general SEER population. The relative risk was substantially higher for malignant mixed mullerian tumors (MMMTs) (O/E = 4.62, O = 34, 95% CI = 3.20 to 6.46) than for endometrial adenocarcinomas (O/E = 2.07, O = 306, 95% CI = 1.85 to 2.32), although the excess absolute risk was smaller—an additional 1.4 versus 8.4 cancers per 10 000 women per year, respectively. Among those who survived for 5 years or longer, there was an eightfold relative risk for MMMTs and a 2.3-fold risk for endometrial adenocarcinomas, with patients developing MMMTs having a worse prognosis. These findings indicate that tamoxifen may have delayed effects, such as the increased risk of MMMTs, rare but aggressive tumors of unclear pathogenesis. [J Natl Cancer Inst 2004;96:70–4]

Tamoxifen has been shown to be effective in improving survival for women with breast cancer and appears to decrease the risk of estrogen receptor–positive breast cancer in high-risk populations of healthy women *(1–4)*. Despite its benefits, tamoxifen has weakly estrogenic properties that can produce endometrial cell proliferation and, consequently, tamoxifen use increases the risk of endometrial cancer by approximately two- to threefold *(5–12)*. Recent studies

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(13–16), including clinical trials in the United States, indicate that the risk associated with tamoxifen may be substantially higher for rare, aggressive forms of uterine tumors, notably malignant mixed mullerian tumors (MMMTs) and uterine sarcomas—observations previously noted in case reports and clinical surveys *(17)*. However, the magnitude of increased risk is unclear. In this report, we extend our previous findings *(18)* and estimate the relative and absolute risk of subsequent malignant uterine tumors by histologic type following tamoxifen therapy for breast cancer.

We analyzed data for women with invasive breast cancer who survived for 1 year or longer and were reported to one of nine population-based cancer registries in the Surveillance, Epidemiology, and End Results (SEER) Program[1] from 1980 through 2000, when adjuvant tamoxifen was widely used. Women given chemotherapy, endocrine surgery, or endocrine radiation therapy as their initial therapy were excluded from the analyses. The 39 451 women who received hormones as their first course of therapy were designated as the "tamoxifen users" on the basis of our previous experience that more than 90% of women given hormones during this period received tamoxifen *(18)*. Therapy given subsequent to the first course of therapy was not available in the SEER database. We then compared the observed number of subsequent uterine corpus cancers that developed among the tamoxifen users to the number expected among the general SEER population. Specifically, the observed-to-expected ratio (O/E) was calculated as the ratio of the number of observed (O) subsequent (including second and third) invasive uterine corpus cancers that developed at least 12 months after diagnosis of invasive female breast cancer to the number expected (E) based on age-, race-, and calendar year–specific SEER incidence rates for uterine corpus cancers. We also computed O/E ratios by histologic type, grade, and stage of uterine corpus cancers. Exact two-sided Poisson-based 95% confidence intervals (CIs) and the excess absolute risk, ([O – E]/woman-years-at-risk) × 10 000, are presented. The cumulative mortality from uterine corpus cancer at 15 years after diagnosis of breast cancer in the presence of competing risks was calculated using death from uterine corpus cancer (cancer of the uterus, not specified as to corpus or cervix) as the event of interest, with all other deaths attributed to the competing risk *(19)*.

We also estimated O/E ratios for a comparison group of patients (referred to as "non–tamoxifen users") treated during a time period when tamoxifen was infrequently used to treat breast cancer. This group consisted of 67 190 breast cancer survivors diagnosed from 1973 through 1979 (for women with all stages of disease) or from 1980 through 1984 (for women with localized stage only). Women who received chemotherapy, hormonal therapy, endocrine surgery, or endocrine radiation therapy were excluded from the analysis. The patient groups designated as "tamoxifen users" and "non–tamoxifen users" were mutually exclusive.

We found that, from 1980 through 2000, breast cancer patients initially treated with tamoxifen had more than a twofold increased risk (O/E = 2.17, 95% CI = 1.95 to 2.41) of developing a subsequent cancer of the uterine corpus when the observed number of subsequent cancers was compared with that expected from the SEER general population (Table 1). However, the relative risk among tamoxifen users was substantially higher for subsequent MMMTs (O/E = 4.62, 95% CI = 3.20 to 6.46) than for endometrial adenocarcinomas (O/E = 2.07, 95% CI = 1.85 to 2.32). Because MMMTs are rare, the large relative risk translates into a small excess absolute increased risk, with only an additional 1.4 tamoxifen-related MMMTs observed per 10 000 woman-years-at-risk, compared with an additional 8.4 tamoxifen-related endometrial adenocarcinomas. We found no evidence of an increased risk of leiomyosarcomas, although we observed a statistically nonsignificant 2.3-fold increase in risk for a combined group of stromal sarcomas and adenosarcomas among tamoxifen users. Among tamoxifen users who survived 5 or more years, the risk of MMMTs was eightfold compared with a 2.3-fold risk for endometrial adenocarcinomas. After the diagnosis of breast cancer, MMMTs tended to be detected later (median time to diagnosis = 7.5 years) than adenocarcinomas (median time to diagnosis = 4.5 years).

We found no increased risk for cancer of the uterine corpus overall (O/E = 0.99, 95% CI = 0.91 to 1.06) or for endometrial adenocarcinomas (O/E = 0.97, 95% CI = 0.90 to 1.06) specifically among non–tamoxifen users treated from 1973 through 1984 (Table 1). However, a statistically nonsignificant increased risk of MMMTs was seen among non–tamoxifen users (O/E = 1.38, 95% CI = 0.97 to 1.91).

We further assessed the risk among subgroups of subsequent endometrial adenocarcinomas. Analyses showed little difference in risk by stage and grade of endometrial adenocarcinoma among tamoxifen users (data not shown). The risk of clear-cell adenocarcinoma was similar among tamoxifen users and non–tamoxifen users. Analysis of serous adenocarcinomas was limited by infrequent reporting of this cancer to SEER before the early 1990s.

The risk of developing endometrial adenocarcinomas and MMMTs among tamoxifen users did not vary appreciably by age at diagnosis or stage of initial breast cancer, although the risk of MMMTs was greatest in women aged 60–69 years at the time of their initial treatment (Table 2). The risk of MMMTs appeared higher for black women (O/E = 8.55, 95% CI = 3.43 to 17.62) than for white women (O/E = 4.11, 95% CI = 2.68 to 6.02), although the difference was not statistically significant.

The cumulative mortality from uterine corpus cancer among tamoxifen users was very low (0.37%, 95% CI = 0.23% to 0.51%) 15 years after initial treatment. Prognosis was poor among patients who developed MMMTs, with 25 deaths among the 34 women diagnosed, including at least 15 deaths attributed to uterine cancer or sarcoma (Table 2). Nonetheless, death related to MMMTs was rare among tamoxifen users, with an estimated 0.8 deaths per 10 000 woman-years-at-risk or approximately 11–12 deaths among 10 000 breast cancer patients followed for 15 years.

Our results from the SEER population-based registries support previous evidence that tamoxifen users have an increased risk of MMMTs *(13–16)*. In U.S. trials of more than 17 000 women, Wickerham et al. *(15)* found that 12 tamoxifen users developed MMMTs or uterine sarcomas (1.7/10 000 woman-years-at-risk) compared with none among non–tamoxifen users. In addition, a Dutch case–control study *(13)* reported that MMMTs and uterine sarcomas were

Table 1. Risk of uterine corpus cancer after breast cancer, by type of initial therapy, histologic type of uterine cancer, and time since breast cancer diagnosis*

	Time since breast cancer diagnosis											
	1–4 y		5–9 y		≥10 y		Total ≥1 y					
No. of patients entering interval*												
Tamoxifen†	39 451		20 053		5522		39 451					
No tamoxifen‡	67 190		51 918		39 050		67 190					
Woman-years at risk												
Tamoxifen	116 191		60 454		11 926		188 571					
No tamoxifen	236 596		224 642		336 526		797 764					
Second uterine cancer/therapy	O	O/E	O	O/E	O	O/E	O	O/E	95% CI	EAR		
All uterine corpus cancers												
Tamoxifen†	193	1.95§	132	2.49§	29	2.72§	354	2.17§	1.95 to 2.41	10.14		
No tamoxifen‡	185	0.98	189	1.05	274	0.95	648	0.99	0.91 to 1.06	−0.12		
Group I. Adenocarcinoma‖												
Tamoxifen¶	176	1.96§	109	2.27§	21	2.19§	306	2.07§	1.85 to 2.32	8.40		
No tamoxifen	168	0.97	173	1.06	241	0.92	582	0.97	0.90 to 1.06	−0.21		
Group II. Malignant mixed mullerian tumors (MMMTs)‖												
Tamoxifen#	10	2.29§	18	7.32§	6	11.52§	34	4.62§	3.20 to 6.46	1.41		
No tamoxifen	9	1.45	8	1.14	19	1.48	36	1.38	0.97 to 1.91	0.12		
Group III. Leiomyosarcomas‖												
Tamoxifen	0	(0.83)**	0	(0.39)**	0	(0.07)**	0	(1.29)**	0.00 to 2.85	−0.07		
No tamoxifen	1	0.44	2	1.10	1	0.44	4	0.63	0.17 to 1.61	−0.03		
Group IV. Endometrial stromal, adenosarcoma‖												
Tamoxifen	2	1.90	1	1.82	1	9.57	4	2.34	0.63 to 5.99	0.12		
No tamoxifen	0	(1.26)**	1	0.67	3	1.05	4	0.71	0.19 to 1.82	−0.02		
Group V. Other uterine corpus cancers‖												
Tamoxifen	5	1.76	4	2.51	1	2.88	10	2.09§	1.00 to 3.84	0.28		
No tamoxifen	7	1.08	5	0.84	10	1.12	22	1.03	0.65 to 1.56	0.01		

*All patients survived 1 or more years following an invasive breast cancer identified through the Surveillance, Epidemiology, and End Results (SEER) Program population registries. Patients who received initial therapy with chemotherapy, endocrine surgery, or endocrine radiation therapy were excluded from the analysis. O = observed number of subsequent (i.e., second and third) cancers; E = expected number of subsequent cancers; O/E = observed-to-expected ratio; tamoxifen group = patients who received hormones as their initial therapy; no-tamoxifen group = patients who did not receive hormones as their initial therapy; CI = confidence interval; EAR = excess absolute risk per 10 000 woman-years-at-risk, ([O − E]/woman-years-at-risk) × 10 000.

†Patients included in the tamoxifen group were diagnosed from 1980 through 2000.

‡Patients included in the no-tamoxifen group were diagnosed from 1973 through 1979 (women with all stages of disease) or from 1980 through 1984 (women with localized stage breast cancer only).

§Statistically significant when 95% CI excludes 1.0.

‖International Classification of Diseases for Oncology (2nd ed.) *(23)* histologic type (morphology) groupings of uterine corpus cancers: Group I. Adenocarcinoma, type I: 8050, 8140–8141, 8143, 8210–8211, 8260–8263, 8323, 8340, 8380–8381, 8440, 8470–8471, 8480–8481, 8490, 8550, 8560, 8570–8573; adenocarcinoma, type II: 8310 clear-cell adenocarcinoma, 8441 serous cystadenocarcinoma, not otherwise specified, 8460–8462 papillary serous cystadenocarcinoma. Group II. Malignant mixed mullerian tumors (MMMT): 8950 mullerian mixed tumor, 8951 mesodermal mixed tumor, 8980 carcinosarcoma, not otherwise specified, 8981 carcinosarcoma, embryonal type. Group III. Leiomyosarcomas 8890–8891, 8896. Group IV. Endometrial stromal, adenosarcoma: 8910 embryonal rhabdomyosarcoma, 8930 endometrial stromal sarcoma, 8933 adenosarcoma. Group V. Other uterine corpus cancers include all other histologic types not included in groups I–IV.

¶Adenocarcinoma tamoxifen group includes one patient with a second papillary serous cystadenocarcinoma and a third endometrioid carcinoma and one patient with a second MMMT (second cancer counted in the MMMT group) and a third serous surface papillary carcinoma (third cancer was counted in the adenocarcinoma group).

#MMMT tamoxifen group includes one patient with a second MMMT (second cancer counted in the MMMT group) and a third serous surface papillary carcinoma (third cancer was counted in the adenocarcinoma group).

**Numbers in parentheses are expected numbers of cancers.

more common among long-term (≥2 years) tamoxifen users than among non–tamoxifen users (15.4% [eight case patients] versus 2.9% [five case patients]). Other studies with smaller numbers of subjects have also suggested that the risk of tamoxifen-related MMMTs is increased *(8,14)* and the time to diagnosis is longer than for tamoxifen-related uterine adenocarcinomas *(17,20)*.

Although mechanisms underlying tamoxifen-related MMMTs are unclear, immunohistochemical and molecular analyses have suggested that MMMTs may originate as an adenocarcinoma that acquires sarcomatous differentiation over time *(21)*. Despite limited epidemiologic evidence that MMMTs and

Table 2. Risk of subsequent uterine corpus cancer following tamoxifen therapy, by age, stage, race, and histologic type of breast cancer, and vital status among patients developing uterine corpus cancer*

Characteristic	No. of patients	Adenocarcinoma			MMMT		
		O	O/E	95% CI	O	O/E	95% CI
Total uterine corpus cancers	39 451	306	2.07†	1.85 to 2.32	34	4.62†	3.20 to 6.46
Age at breast cancer diagnosis, y							
<50	3002	12	2.33†	1.20 to 4.06	0	(0.10)‡	0.00 to 36.11
50–59	7053	46	1.78†	1.30 to 2.37	3	3.57	0.72 to 10.43
60–69	11 553	118	2.07†	1.72 to 2.48	18	6.91†	4.09 to 10.91
≥70	17 843	130	2.18†	1.82 to 2.59	13	3.42†	1.82 to 5.84
Stage at breast cancer diagnosis							
Localized	25 142	178	1.97†	1.69 to 2.29	23	5.34†	3.38 to 8.01
Regional	11 045	110	2.21†	1.82 to 2.66	10	3.82†	1.83 to 7.02
Distant	2302	11	2.31†	1.15 to 4.14	1	3.98	0.05 to 2.22
Unstaged	962	7	2.41	0.97 to 4.97	0	(0.17)‡	0.00 to 21.05
Race							
White	34 702	275	2.00†	1.77 to 2.26	26	4.11†	2.68 to 6.02
Black	2273	9	1.83	0.83 to 3.47	7	8.55†	3.43 to 17.62
Other	2405	22	4.78†	3.00 to 7.24	1	5.14	0.07 to 28.59
		No.	%		No.	%	
Vital status§		305	100.0		34	100.0	
Total alive		174	57.1		9	26.5	
Total dead		131	42.9		25	73.5	
Uterine cancer deaths‖		29	9.5		15	44.1	

*All patients survived 1 or more years following invasive breast cancer diagnosed from 1980 through 2000. Patients who received hormonal therapy (tamoxifen) as their initial therapy. Patients who received initial therapy in the form of chemotherapy, endocrine surgery, or endocrine radiation therapy were excluded from the analyses. All patients were identified from the Surveillance, Epidemiology, and End Results (SEER) Program population registries. MMMT = malignant mixed mullerian tumor; O = observed number of subsequent (e.g., second and third) cancers; E = expected number of subsequent cancers; O/E = observed-to-expected ratio.

†Statistically significant when 95% confidence interval excludes 1.0.

‡Numbers in parentheses are expected numbers of uterine corpus cancers.

§Vital status of breast cancer patients who developed uterine corpus cancer as their second cancer. Number of patients with uterine adenocarcinomas (n = 305) excludes one patient who had a second MMMT uterine tumor and a third uterine adenocarcinoma.

‖Includes deaths due to uterine cancer or sarcoma.

endometrial carcinomas may share reproductive and hormonal risk factors *(22)*, the delayed time to diagnosis and more aggressive behavior associated with tamoxifen-related MMMTs relative to endometrial adenocarcinomas in our study and other investigations *(13,16)* suggest differences in pathogenic mechanisms.

An advantage of our study was the large number of breast cancer patients treated with hormones in a population-based setting. However, we were limited by a lack of information regarding tamoxifen dose and duration of use, therapy for recurrences, hysterectomy data, use of postmenopausal estrogens, and other risk factors for endometrial cancer. In addition, our estimates of secondary cancer risk may be conservative because cancer diagnoses are not available for those patients who migrate out of SEER catchment areas. However, risks may also be affected by increased surveillance and detection bias among tamoxifen users.

In conclusion, we provide population-based evidence that use of tamoxifen is associated with an overall fourfold relative risk for MMMTs, which rose to eightfold among long-term breast cancer survivors, compared with the twofold risk for endometrial adenocarcinomas. Although MMMTs are associated with a poor prognosis, these tumors are rare and the absolute risk of death is small. These findings indicate that tamoxifen may have delayed effects in some patients, such as the heightened risk of MMMTs, aggressive tumors of unclear pathogenesis.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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